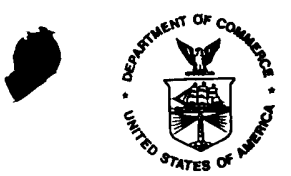

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/330,929	06/02/99	KLEINSCHMIDT	J 4121-107

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KER, J	
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DATE MAILED: 01/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/230,929	Kleinschmidt et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

X Responsive to communication(s) filed on *Nov 2, 2000*.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *14-66* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *14-66* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicants' amendment, filed 11/2/00, has been entered.

Claims 1-13 have been canceled.

Claims 14-66 have been added.

Applicant's election of Group I in Paper No. 10 is acknowledged. As the vaccines of Group II require the same vector as that in the invention of Group I, the non-elected claims have been rejoined. Claims 14-66 are being examined on the merits.

Specification

Abstract

The abstract of the disclosure is objected to because it should only have one paragraph, however, the instant abstract contains two paragraphs. Correction is required. See MPEP § 608.01(b).

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Applicants should amend the specification to include the appropriate section headings in the appropriate locations of the specification.

Objections to the Disclosure

The disclosure is objected to because of the following informalities: the phrase "associated to papilloma viruses" on pages 1, 2, 4, and 5 is confusing as it is unclear what is meant by "associated to"; it is unclear what is meant by the term "benignant" on page 1; and it is unclear what is meant by the phrase "possible for it the integration" on page 2. In addition, the term "respectively" is used throughout the specification, however, it is unclear how this term is being used. For example, on page 3, the specification states "A preferred (poly)peptide is coded by E6-ORF or E7-ORF of a papilloma virus and by part thereof, respectively.". As another example, on page 5, the specification states, "The present invention represents a new step of treating the most severe diseases via an *in vivo* gene therapy and *ex vivo* gene therapy, respectively.". It is not clear how the term "respectively" relates to the prior information in the sentence. Furthermore, the specification appears to be inconsistent with respect to the function of the E6 and E7 proteins. For example, on page 1, the specification states that "The transformation ability of papilloma viruses is ascribed to the proteins E6 and E7. They are coded by E6-ORF and E7-ORF, respectively.". However, on page 3, the specification states "The expression "non-transforming" refers to the fact that the (poly)peptide has no transformation ability by nature or by intervention.

A preferred (poly)peptide is coded by E6-ORF or E7-ORF of a papilloma virus and by part thereof, respectively.". These statements appear to be conflicting. Clarification is requested.

Appropriate correction is required.

Claim Objections

Claim 66 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 66 recites the limitation that "the fusion polypeptide is administered as a component of a vaccine composition". However, claim 65, upon which claim 66 depends, is directed to administration of an adenovirus vector comprising a nucleotide sequence encoding a fusion polypeptide, not administration of a fusion polypeptide. As written, claim 66 expands rather than limits the subject matter of claim 65. If applicants intended that the vector is administered as a component of a vaccine composition, then applicants should amend the claim accordingly.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition comprising the adeno-associated virus vector as set forth in claim 14 and an auxiliary agent, does not reasonably provide enablement for a vaccine

composition wherein the vector is provided as a component of a cell, wherein the cell is a tumor or pre-tumor cell and is associated with human papilloma virus infection, and wherein the cell is inactivated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection.

The claims are directed to a vaccine composition comprising the adeno-associated virus vector as set forth in claim 14 and an auxiliary agent, wherein the vector is provided as a component of the cell (claim 62), wherein the cell is a tumor or pre-tumor cell and is associated with human papilloma virus infection (claim 63), and wherein the cell is inactivated (claim 64).

While the specification discloses an adeno-associated virus vector comprising a polynucleotide encoding a fusion protein comprising L1 or L2 and any one of E1, E2, E4, E5, E6, or E7 papilloma virus proteins, and wherein the adeno-associated virus vector can be used as a vaccine, the specification does not disclose a vaccine composition wherein the vector is provided as a component of a cell, wherein the cell is a tumor or pre-tumor cell and is associated with human papilloma virus infection, and wherein the cell is inactivated. The specification does not provide any guidance as to how to make or use a vaccine composition wherein the vector is provided as a component of a cell. In addition, it is not readily apparent from the specification what is meant by "tumor or pre-tumor cells which are associated with human papilloma virus infection". There is no disclosure of a type of association between a tumor or pre-tumor cell and a human papilloma virus infection. Moreover, with respect to inactivation of a cell, the specification neither defines nor describes how to "inactivate" the cell. By inactivation, did applicants intend killing the cells? In addition, there is no teaching in the specification as to how one of skill in the art would use such vaccine compositions such that an immunogenic response would be obtained, i.e., there is no guidance as to how to deliver such cellular vaccine

compositions with respect to routes of administration or dosages, nor are there any working examples which provide such guidance and further establish that the delivered compositions are effective as vaccines. In addition, the specification does not incorporate by reference any prior art which provides the necessary information to make and use the cellular vaccine compositions. In view of the lack of guidance in the specification and the lack of working examples, one of skill in the art would not know how to make and use the invention as claimed without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-48, 51, 52, and 60-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 26, 28, 31, 33, 35, 37, 39, 41, 43-48, 51, 52, and 65 are rendered vague and indefinite by the term "fragment(s)" as there is no definition in the specification or the claims as to what size and which amino acids of the papilloma virus proteins constitute a "fragment" required in the claimed invention. The metes and bounds of the claims are unclear.

Claim 14 is rendered vague and indefinite by the phrase "L1-ORF and L2-ORF, and fragments" as this is improper Markush language. Only one "and" should appear in a proper Markush group. It is suggested that applicants delete the first "and" of the phrase to overcome this rejection.

Claims 61 and 62 are rendered vague and indefinite by the phrase "The vaccine composition of claim 49" as there is no vaccine composition recited in claim 49. The phrase lacks antecedent basis.

Claim 62 is further rendered vague and indefinite by the phrase "wherein the vector is provided as a component of a cell" as it is unclear how a vector is provided as a cell component, i.e., which cellular component is the vector?

Claim 63 is rendered vague and indefinite by the phrase "wherein the cell is a tumor or pre-tumor cell and is associated with human papilloma virus infection" as it is unclear what type of association is intended. The claim is confusing.

Claim 64 is rendered vague and indefinite by the phrase "wherein the cell is inactivated" as it is unclear what is meant by "inactivated", i.e., did applicants intend that the cell is killed? It is unclear what applicants are claiming.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Claims 14-25, 27-30, 32, 34, 36, 38, 40, 42-60, 65, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* (WO 96/00583, 1/11/96), taken with Johnson (U.S. Patent No. 5,658,785, 8/19/97, effective filing date of 6/6/94, newly applied).

Donnelly *et al.* teach vaccines comprising DNA constructs encoding papilloma virus gene products which are capable of being expressed upon direct introduction into animal tissues, and novel prophylactic and therapeutic pharmaceuticals which can provide immune protection against infection by papilloma virus (see, e.g., page 6, lines 8-11 and page 8, lines 1-10). The protective efficacy of DNA vaccination against subsequent viral challenge is demonstrated by immunization with non-replicating plasmid DNA encoding one or more of the viral proteins (see, e.g., page 5, lines 29-32). The polynucleotide vaccine can encode the PV proteins such as L1 or L2 or E1 through E7 or combinations thereof or can encode proteins of HPV types 6a, 6b, 11, 16, or 18 (see, e.g., page 12, lines 9-31 and claims 1-6). The vaccines comprise HPV DNA that encode recombinant proteins of HPV that contain the antigenic determinants that induce the formation of neutralizing antibodies in the human host. The vaccines can be monovalent, e.g., a monovalent HPV type 16 vaccine can be made by formulating DNA encoding HPV 16 L1 protein or L2 protein or L1+L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding HPV L1 or L2 or L1+L2 proteins from different HPV types (see, e.g., page 14, lines 3-10). In addition, Donnelly *et al.* teach methods of administration of the vaccine (see, e.g., page 13, lines 6-32, and page 14, lines 1-2). Thus, Donnelly *et al.* teach a vaccine comprising polynucleotides encoding L1 or L2 or E1 through E7 papilloma virus proteins or combinations thereof (e.g., fusion polypeptides), wherein the papilloma virus can be human papilloma virus of various types, such as 6a, 6b, 11, 16, or 18 and methods of administration.

Donnelly *et al.* do not teach an adeno-associated virus (AAV) vector comprising the papilloma virus polynucleotides encoding fusion polypeptides. However, Johnson teaches AAV vectors comprising a constitutive or inducible promoter (which the specification equates to a tissue-specific or tumor-specific promoter, see page 3, lines 2-4 of the specification), which are suitable for delivering foreign DNA to cells, including that obtained from pathogens, and which

can be used for genetic immunization, i.e., as vaccines (see, e.g., column 3, lines 33-41, and column 4, lines 20-36 and lines 49-53). Johnson further teaches that the vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism by administering to the host an immunity-inducing amount of the recombinant AAV vector which encodes the polypeptide (see, e.g., column 5, lines 5-33). Johnson teaches that methods of genetic immunization including direct DNA injection or infection with retroviral vectors are known in the art, direct DNA inoculation may not provide long-lasting immune responses and serious questions of safety surround the use of retroviral vectors and that the use of AAV vector for genetic immunization is not subject to these problems. In addition, Johnson teaches that AAV vectors possess unique features that make it attractive as a vector for delivering foreign DNA to cells, e.g., AAV infection of cells in culture is noncytopathic, natural infection of humans and other animals is silent and asymptomatic, and AAV infects most, if not all, mammalian cells allowing the possibility of targeting many different tissues *in vivo* (see, e.g., column 1, lines 49-67 and column 2, lines 1-50).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the papilloma virus DNA vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into the AAV vector of Johnson in view of the teachings of Johnson that AAV vectors comprising immunogenic polypeptides are suitable as vaccines for stimulating an immune response. One of ordinary skill in the art would have been motivated to modify the vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into an AAV vector in view of the teachings of Johnson that use of the AAV vector in genetic immunization overcomes the disadvantages of direct inoculation of DNA or infection with retroviral vectors. Moreover, in view of the teachings of Johnson that the AAV vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism, one of ordinary skill in the art would have had a high expectation of successfully making an AAV vaccine vector taught by Johnson comprising a polynucleotide which encodes the human papilloma virus fusion proteins taught by Donnelly *et*

al., and using the resultant AAV vaccine for generating intracellular or systemic immunity in a person in need thereof.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 14-60, 65, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* (WO 96/00583, 1/11/96), taken with Johnson (U.S. Patent No. 5,658,785, 8/19/97, effective filing date of 6/6/94, newly applied) as applied to claims 14-25, 27-30, 32, 34, 36, 38, 40, 42-60, 65, and 66 above, and further in view of Whittle *et al.* (U.S. Patent No. 5,955,087, 9/21/99, effective filing date of 6/8/95, newly applied).

This rejection applies to the claims directed to adeno-associated virus vectors comprising polynucleotides encoding HPV fusion proteins, wherein the fusion proteins comprise fragments of the polypeptides of (a) and (b).

Donnelly *et al.* teach that different HPV types cause distinct diseases. Donnelly *et al.* further teach vaccines comprising DNA constructs encoding papilloma virus gene products which are capable of being expressed upon direct introduction into animal tissues, and novel prophylactic and therapeutic pharmaceuticals which can provide immune protection against infection by papilloma virus (see, e.g., page 6, lines 8-11 and page 8, lines 1-10). The protective efficacy of DNA vaccination against subsequent viral challenge is demonstrated by immunization with non-replicating plasmid DNA encoding one or mor of the viral proteins (see, e.g., page 5, lines 29-32). The polynucleotide vaccine can encode the PV proteins such as L1 or L2 or E1 through E7 or combinations thereof or can encode proteins of HPV types 6a, 6b, 11, 16, or 18 (see, e.g., page 12, lines 9-31 and claims 1-6). The vaccines comprise HPV DNA that encode recombinant proteins of HPV that contain the antigenic determinants that induce the formation of neutralizing antibodies in the human host. The vaccines can be monovalent, e.g., a monovalent HPV type 16 vaccine can be made by formulating DNA encoding HPV 16 L1 protein or L2

protein or L1+L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding HPV L1 or L2 or L1+L2 proteins from different HPV types (see, e.g., page 14, lines 3-10). In addition, Donnelly *et al.* teach methods of administration of the vaccine (see, e.g., page 13, lines 6-32, and page 14, lines 1-2). Thus, Donnelly *et al.* teach a vaccine comprising polynucleotides encoding L1 or L2 or E1 through E7 papilloma virus proteins or combinations thereof (e.g., fusion polypeptides), wherein the papilloma virus can be human papilloma virus of various types, such as 6a, 6b, 11, 16, or 18 and methods of administration.

Donnelly *et al.* do not teach an adeno-associated virus (AAV) vector comprising the papilloma virus polynucleotides encoding fusion polypeptides. However, Johnson teaches AAV vectors comprising a constitutive or regulatable promoter (which the specification equates to a tissue-specific or tumor-specific promoter, see page 3, lines 2-4 of the specification), which are suitable for delivering foreign DNA to cells, including that obtained from pathogens, and which can be used for genetic immunization, i.e., as vaccines (see, e.g., column 3, lines 33-41, and column 4, lines 20-36 and lines 49-53). Johnson further teaches that the vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism by administering to the host an immunity-inducing amount of the recombinant AAV vector which encodes the polypeptide (see, e.g., column 5, lines 5-33). Johnson teaches that methods of genetic immunization including direct DNA injection or infection with retroviral vectors are known in the art, direct DNA inoculation may not provide long-lasting immune responses and serious questions of safety surround the use of retroviral vectors and that the use of AAV vector for genetic immunization is not subject to these problems. In addition, Johnson teaches that AAV vectors possess unique features that make it attractive as a vector for delivering foreign DNA to cells, e.g., AAV infection of cells in culture is noncytopathic, natural infection of humans and other animals is silent and asymptomatic, and AAV infects most, if not all, mammalian cells allowing the possibility of targeting many different tissues *in vivo* (see, e.g., column 1, lines 49-67 and column 2, lines 1-50).

The above references do not teach polynucleotides encoding fusion proteins comprising fragments of the L1, L2, E1, E2, E4, E5, E6, and E7 papilloma virus proteins. However, Whittle *et al.* teach fusion polypeptides that combine papilloma-virus-derived antigens from at least two different papilloma virus proteins, e.g., at least an antigenic determinant of a papilloma virus L2 protein and at least an antigenic determinant selected from E1, E2, E4, E5, E6, and E7 papilloma virus proteins and L2 papilloma virus proteins of different papilloma virus type from which E1, E2, E4, E5, E6, and E7 proteins are obtained. The polypeptides can compositions thereof comprise antigenic determinants of human papilloma virus proteins from HPV types 6, 11, 16, and 18, although antigenic determinants of proteins from other HPV types are suitable. Furthermore, the antigenic determinant can be either the full sequence of the protein of interest, or by a fragment, such as an N-terminal or C-terminal fragment of the protein (see, e.g., column 3, lines 30-67, and the claims). The antigenic determinants can be from part of a fusion polypeptide selected from the L1, L2, E1, E2, E4, E5, E6, and E7 proteins. The polypeptide can comprise at least an antigenic determinant from each of at least two different proteins, and from the same or from different papilloma virus types. At least one of the proteins can be selected from L1 or L2 and/or at least one of the proteins can be selected from E1, E2, E4, E5, E6, and E7 (see, e.g., column 4, lines 1-27). Whittle *et al.* also teach vectors comprising nucleic acids which encode the proteins and which express the proteins in a host cells (see, e.g., Examples 1-4, and 9-11).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the papilloma virus DNA vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into the AAV vector of Johnson in view of the teachings of Johnson that AAV vectors comprising immunogenic polypeptides are suitable as vaccines for stimulating an immune response. One of ordinary skill in the art would have been motivated to modify the vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into an AAV vector in view of the teachings of Johnson that use of the AAV vector in genetic immunization overcomes the disadvantages of direct inoculation of DNA or infection with retroviral vectors. Moreover, in view of the teachings of Johnson that the AAV vaccine vector can be used to

generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism, one of ordinary skill in the art would have had a high expectation of successfully making an AAV vaccine vector taught by Johnson comprising a polynucleotide which encodes the human papilloma virus fusion proteins taught by Donnelly *et al.*, and using the resultant AAV vaccine for generating intracellular or systemic immunity in a person in need thereof. It would have further been obvious to substitute polynucleotides encoding full length papilloma virus proteins with polynucleotides encoding the protein fragments taught by Whittle *et al.* in view of the teachings of Whittle *et al.* that such protein fragments are immunogenic.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 16, 18, 20, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* (WO 96/00583, 1/11/96), taken with Johnson (U.S. Patent No. 5,658,785, 8/19/97, effective filing date of 6/6/94, newly applied) as applied to claims 14-25, 27-30, 32, 34, 36, 38, 40, 42-60, 65, and 66 above, and further in view of Gissmann *et al.* (WO 96/11272, 4/18/96, newly applied).

This rejection applies to the claims directed to adeno-associated virus vectors comprising polynucleotides encoding HPV fusion proteins, wherein the fusion proteins are full length proteins or fragments thereof obtained from the L1, L2, E1, E2, E4, E5, E6, and E7 human papilloma virus proteins and wherein the HPV types include HPV 33, HPV 35 and HPV 45.

Donnelly *et al.* teach that different HPV types cause distinct diseases. Donnelly *et al.* further teach vaccines comprising DNA constructs encoding papilloma virus gene products which are capable of being expressed upon direct introduction into animal tissues, and novel prophylactic and therapeutic pharmaceuticals which can provide immune protection against infection by papilloma virus (see, e.g., page 6, lines 8-11 and page 8, lines 1-10). The protective

efficacy of DNA vaccination against subsequent viral challenge is demonstrated by immunization with non-replicating plasmid DNA encoding one or mor of the viral proteins (see, e.g., page 5, lines 29-32). The polynucleotide vaccine can encode the PV proteins such as L1 or L2 or E1 through E7 or combinations thereof or can encode proteins of HPV types 6a, 6b, 11, 16, or 18 (see, e.g., page 12, lines 9-31 and claims 1-6). The vaccines comprise HPV DNA that encode recombinant proteins of HPV that contain the antigenic determinants that induce the formation of neutralizing antibodies in the human host. The vaccines can be monovalent, e.g., a monovalent HPV type 16 vaccine can be made by formulating DNA encoding HPV 16 L1 protein or L2 protein or L1+L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding HPV L1 or L2 or L1+L2 proteins from different HPV types (see, e.g., page 14, lines 3-10). In addition, Donnelly *et al.* teach methods of administration of the vaccine (see, e.g., page 13, lines 6-32, and page 14, lines 1-2). Thus, Donnelly *et al.* teach a vaccine comprising polynucleotides encoding L1 or L2 or E1 through E7 papilloma virus proteins or combinations thereof (e.g., fusion polypeptides), wherein the papilloma virus can be human papilloma virus of various types, such as 6a, 6b, 11, 16, or 18 and methods of administration.

Donnelly *et al.* do not teach an adeno-associated virus (AAV) vector comprising the papilloma virus polynucleotides encoding fusion polypeptides. However, Johnson teaches AAV vectors comprising a constitutive or regulatable promoter (which the specification equates to a tissue-specific or tumor-specific promoter, see page 3, lines 2-4 of the specification), which are suitable for delivering foreign DNA to cells, including that obtained from pathogens, and which can be used for genetic immunization, i.e., as vaccines (see, e.g., column 3, lines 33-41, and column 4, lines 20-36 and lines 49-53). Johnson further teaches that the vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism by administering to the host an immunity-inducing amount of the recombinant AAV vector which encodes the polypeptide (see, e.g., column 5, lines 5-33). Johnson teaches that methods of genetic immunization including direct DNA injection or infection with retroviral vectors are known in the art, direct DNA inoculation may not provide

long-lasting immune responses and serious questions of safety surround the use of retroviral vectors and that the use of AAV vector for genetic immunization is not subject to these problems. In addition, Johnson teaches that AAV vectors possess unique features that make it attractive as a vector for delivering foreign DNA to cells, e.g., AAV infection of cells in culture is noncytopathic, natural infection of humans and other animals is silent and asymptomatic, and AAV infects most, if not all, mammalian cells allowing the possibility of targeting many different tissues *in vivo* (see, e.g., column 1, lines 49-67 and column 2, lines 1-50).

The above references do not teach that the polynucleotides encode fusion proteins obtained from HPV types 33, 35, or 45. However, Gissmann *et al.* teach recombinant papilloma virus fusion proteins comprising L1- or L2- protein and E1, E2, E4, E5, E6 and/or E7 wherein the DNA encoding the fusion proteins can be incorporated into vectors such as vaccinia, baculovirus, or bacterial vector systems (see, e.g., page 13, lines 5-22). In addition, Gissmann *et al.* teach fusion proteins comprising a fragment of L1, and fusion proteins wherein the L1, L2, E1, E2, E4, E5, E6, and E7 proteins are from human papilloma virus 6, 11, 16, 18, 33, 35, or 45 (see, e.g., page 13, lines 29-36, and page 16, lines 4-35. In addition, Gissmann *et al.* teach that the fusion proteins can be used as vaccines, see, e.g. page 6, lines 14-20.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the papilloma virus DNA vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into the AAV vector of Johnson in view of the teachings of Johnson that AAV vectors comprising immunogenic polypeptides are suitable as vaccines for stimulating an immune response. One of ordinary skill in the art would have been motivated to modify the vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into an AAV vector in view of the teachings of Johnson that use of the AAV vector in genetic immunization overcomes the disadvantages of direct inoculation of DNA or infection with retroviral vectors. Moreover, in view of the teachings of Johnson that the AAV vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism, one of ordinary skill in the art would have had a high

expectation of successfully making an AAV vaccine vector taught by Johnson comprising a polynucleotide which encodes the human papilloma virus fusion proteins taught by Donnelly *et al.*, and using the resultant AAV vaccine for generating intracellular or systemic immunity in a person in need thereof. It would have further been obvious to substitute polynucleotides encoding full length papilloma virus proteins with polynucleotides encoding the protein fragments taught by Gissmann *et al.* in view of the teachings of Gissmann *et al.* that such protein fragments are immunogenic.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* (WO 96/00583, 1/11/96), taken with Johnson (U.S. Patent No. 5,658,785, 8/19/97, effective filing date of 6/6/94, newly applied) as applied to claims 14-25, 27-30, 32, 34, 36, 38, 40, 42-60, 65, and 66 above, and further in view of Stanley *et al.* (U.S. Patent No. 6,096,869, 8/1/00, effective filing date of 3/22/96, newly applied).

Donnelly *et al.* teach that different HPV types cause distinct diseases. Donnelly *et al.* further teach vaccines comprising DNA constructs encoding papilloma virus gene products which are capable of being expressed upon direct introduction into animal tissues, and novel prophylactic and therapeutic pharmaceuticals which can provide immune protection against infection by papilloma virus (see, e.g., page 6, lines 8-11 and page 8, lines 1-10). The protective efficacy of DNA vaccination against subsequent viral challenge is demonstrated by immunization with non-replicating plasmid DNA encoding one or mor of the viral proteins (see, e.g., page 5, lines 29-32). The polynucleotide vaccine can encode the PV proteins such as L1 or L2 or E1 through E7 or combinations thereof or can encode proteins of HPV types 6a, 6b, 11, 16, or 18 (see, e.g., page 12, lines 9-31 and claims 1-6). The vaccines comprise HPV DNA that encode

recombinant proteins of HPV that contain the antigenic determinants that induce the formation of neutralizing antibodies in the human host. The vaccines can be monovalent, e.g., a monovalent HPV type 16 vaccine can be made by formulating DNA encoding HPV 16 L1 protein or L2 protein or L1+L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding HPV L1 or L2 or L1+L2 proteins from different HPV types (see, e.g., page 14, lines 3-10). In addition, Donnelly *et al.* teach methods of administration of the vaccine (see, e.g., page 13, lines 6-32, and page 14, lines 1-2). Thus, Donnelly *et al.* teach a vaccine comprising polynucleotides encoding L1 or L2 or E1 through E7 papilloma virus proteins or combinations thereof (e.g., fusion polypeptides), wherein the papilloma virus can be human papilloma virus of various types, such as 6a, 6b, 11, 16, or 18 and methods of administration.

Donnelly *et al.* do not teach an adeno-associated virus (AAV) vector comprising the papilloma virus polynucleotides encoding fusion polypeptides. However, Johnson teaches AAV vectors comprising a constitutive or regulatable promoter (which the specification equates to a tissue-specific or tumor-specific promoter, see page 3, lines 2-4 of the specification), which are suitable for delivering foreign DNA to cells, including that obtained from pathogens, and which can be used for genetic immunization, i.e., as vaccines (see, e.g., column 3, lines 33-41, and column 4, lines 20-36 and lines 49-53). Johnson further teaches that the vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism by administering to the host an immunity-inducing amount of the recombinant AAV vector which encodes the polypeptide (see, e.g., column 5, lines 5-33). Johnson teaches that methods of genetic immunization including direct DNA injection or infection with retroviral vectors are known in the art, direct DNA inoculation may not provide long-lasting immune responses and serious questions of safety surround the use of retroviral vectors and that the use of AAV vector for genetic immunization is not subject to these problems. In addition, Johnson teaches that AAV vectors possess unique features that make it attractive as a vector for delivering foreign DNA to cells, e.g., AAV infection of cells in culture is noncytopathic, natural infection of humans and other animals is silent and asymptomatic, and

AAV infects most, if not all, mammalian cells allowing the possibility of targeting many different tissues *in vivo* (see, e.g., column 1, lines 49-67 and column 2, lines 1-50).

The above references do not teach the AAV papilloma virus vaccine composition further comprising one or more immune system activating agents. However, Stanley *et al.* teach a pharmaceutical treatment material comprising a combination of IL-12 for use as a vaccine adjuvant (i.e., an immune system activating agent) and a vector encoding and able to cause expression of a papilloma virus antigen for use as a vaccine. The vector can encode at least one papilloma virus protein or antigenic fragment or fusion protein corresponding thereto. For example, the vector can encode a polypeptide with at least a substantial part of the sequence of at least one papilloma virus protein E1, E2, E4, E5, E6, L1, and/or L2 of HPV 6, 11, 16 and/or 18 (see, e.g., column 3, lines 48-67 and column 4, lines 1-3).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the papilloma virus DNA vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into the AAV vector of Johnson in view of the teachings of Johnson that AAV vectors comprising immunogenic polypeptides are suitable as vaccines for stimulating an immune response. One of ordinary skill in the art would have been motivated to modify the vaccine of Donnelly *et al.* by incorporating the papilloma virus DNA into an AAV vector in view of the teachings of Johnson that use of the AAV vector in genetic immunization overcomes the disadvantages of direct inoculation of DNA or infection with retroviral vectors. Moreover, in view of the teachings of Johnson that the AAV vaccine vector can be used to generate intracellular or systemic immunity and that the host can be immunized against a polypeptide of a disease-causing organism, one of ordinary skill in the art would have had a high expectation of successfully making an AAV vaccine vector taught by Johnson comprising a polynucleotide which encodes the human papilloma virus fusion proteins taught by Donnelly *et al.*, and using the resultant AAV vaccine for generating intracellular or systemic immunity in a person in need thereof. Moreover, it would have further been obvious to include in the papilloma virus vaccine composition an immune system activating agent in view of the teachings of Stanley

et al. of pharmaceutical vaccine compositions comprising a vector encoding papilloma virus proteins or fusion proteins thereof in combination with the adjuvant, IL-12.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

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